Cervicofacial cellulitis: The impact of non-steroidal anti-inflammatory drugs. A study of 70 cases

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Abstract

Introduction: Cervicofacial cellulitis (CFC) is a severe infection of the subcutaneous cellular tissue, and is one of the most serious head and neck infectious emergencies. In a series of 70 cases treated between 2007 and 2012, we noticed a strong correlation between use of non-steroidal anti-inflammatory drugs (NSAIDs) and evolution of head and neck infections toward CFC, including two cases of necrotic CFC extending to the mediastinum, which were fatal.

Material and methods: The cases included in the series comprised patients admitted to emergency and requiring hospitalization due to the severity of presenting symptoms. There were 70 such cases of CFC between 2007 and 2012; cases managed on an outpatient basis were excluded, as were cases of orbital CFC, CFC of sinus origin and mastoiditis.

Results: Eighty percent of patients took NSAIDs, on self-medication or by prescription (community physician, dentist, pharmacist). The most frequent molecules were tiaprofenic acid and diclofenac. CFC extension was restricted in most cases to the maxillary and/or ipsilateral subhyoid region, with 5 cases of lower cervical extension and 2 of mediastinal involvement, which both proved fatal.

Conclusion: CFC is a severe infection that can be life-threatening, and represents a diagnostic and therapeutic emergency. Among other risk factors, use of NSAIDs is frequently reported; these should therefore be used with caution if at all in head and neck infection, especially of odonto-stomatological origin.

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1. Introduction

Cervicofacial cellulitis (CFC) is one of the most frequent head and neck infectious emergencies and also one of the most serious. Mortality is non-negligible despite diagnostic and therapeutic progress.

It is an infection of the cellulo-adipose spaces of the head and neck, mainly of oro-dental (70%) or oropharyngeal (20%) origin [1,2]. Most cases are localized acute forms without signs of severity (serous and suppurring forms), rapidly resolved by correct medical and surgical management, but others may be life-threatening due to rapid spread causing extensive cellulitis that may involve the mediastinum, or to particular aggressiveness, with extensive necrosis (necrotizing fasciitis).

Nosologically, the term “necrotizing fasciitis” is used in English as a generic term for all types of cellulitis, whereas the term “cellulitis” actually covers a very wide range of pathologies, from purulence to extensive necrosis, the latter being the object of the French term fasciite nécrosante.

Severe forms may be due to incomplete or unsuitable treatment (anti-biotherapy not adapted to bacteriology, insufficient surgical resection of necrotic tissue) or to an underlying predisposition impairing the organism’s defenses (diabetes, congenital or acquired immune deficiency).

As well as these known risk factors, overprescription of non-steroidal anti-inflammatory drugs (NSAIDs) has frequently been reported as associated with complications in CFC, although the causal link has not been definitively established.

In our practice in the ENT and Head and Neck Surgery Department of the Specialties Hospital of Rabat (Morocco), we regularly noticed a high frequency of NSAID use by patients presenting CFC requiring hospitalization. This clinical observation underlay the present prospective cohort study covering a 5-year period, to determine the impact of NSAIDs on the evolution of CFC.
2. Patients and methods

A prospective study was performed between, September 2007 and January 2012, in the ENT and H&N Surgery department of the Specialties Hospital of Rabat (Morocco).

Patients admitted to the Emergency Department of the Rabat Specialities Hospital for CFC and hospitalized due to the severity of their presenting symptoms were included. The numerous cases that could be managed on an outpatient basis were excluded for organizational reasons: loss to follow-up, missing data, etc.

Data were collected on a form detailing, among other points:

- probable or proven origin of infection (dental, oral, oropharyngeal, adenitis, etc.);
- NSAID intake in the period preceding CFC onset: molecule, dose, treatment duration and prescription modalities (self-medication, specialist or non-specialist medical prescription);
- risk factors: diabetes, long-course corticotherapy, other immune deficiency factors;
- pre- and post-admission assessment: blood tests, bacteriology, contrast-enhanced CT, and management after admission (surgery, intensive care).

3. Results

Between 2007 and 2012, 70 patients were recruited: 43 male, 27 female (sex ratio 1.59); age ranging from 8 to 65 years old (median age 33 years).

Fifteen files lacked data (pre-assessment use of undetermined self- or prescription-medication) and were therefore excluded.

3.1. History

Nineteen patients had type-2 diabetes (27.41%), all with poor glycemic control at admission (glycemia > 2 g/dL). In 5 patients, the CFC revealed the diabetes.

There were no cases of long-course corticotherapy or of congenital or acquired immune deficiency.

3.2. Functional symptomatology

Dental pain or treatment in the days preceding symptom onset was reported in 53 patients (75.7%). These patients showed limitations in mouth opening of varying severity, this being part of the reasons for admission. All had pain, exacerbated on palpation, at the CFC site; there was little fever, probably due to NSAIDs or paracetamol.

3.3. Origin of CFC

CFC origin was dental in 61 patients (87.14%), suggested by the patient at admission or on interview in terms of dental pain or treatment (53 patients).

This was confirmed clinically by findings of tooth decay or residual root, and/or radiologically by systematic pantomogram revealing dental origin in the patients without dental presenting symptoms.

CFC origin was presumed to be tonsillar in 2 cases. Adenitis was implicated in 1 case. Origin was undetermined in 6 cases.

3.4. Associated signs

Forty-seven patients showed limitation of mouth opening (67.14% of the overall series and 77.05% of CFCs of dental origin); 11 presented an edema of the floor of the mouth and 5 had slight dysphagia. Impact on general health status was moderate in all cases.

3.5. CFC site and extension

CFC was restricted to the maxillary and superolateral cervical regions in 60 patients (85%).

Tumefaction was hard, pre-collected without skin inflammation in 22 cases, and fluctuating, with skin inflammation, in 48.

Extension was toward the temporal region in 3 cases, and the inferolateral cervical region in 5. There was mediastinal involvement in 2 patients, who had taken NSAIDs, with fatal outcome despite intensive care (Fig. 1).

3.6. Assessment

Standard biological assessment systematically comprised complete blood count and electrolyte analysis, screening for glycemic variability and associated hydroelectrolytic disorder.

A sample was taken for bacteriology whenever a purulent gathering was located, including in patients taking antibiotics before admission. In 10 cases (10.83%), multi-bacterial flora was found, comprising cocci and Gram-negative bacilli.

Sixty-one patients underwent pantomography, and contrast enhanced CT was performed systematically to screen for purulence and assess deep extension.

3.7. Pre-admission treatments

NSAIDs were being taken by 56 patients (80%).

The two most frequently prescribed molecules were tiaprofenic acid and diclofenac, in association in some cases.

In addition to NSAIDs, all patients had been taking one or more antibiotics before admission to emergency, prescribed by their community physician (n = 22), dentist (n = 19) or specialist (n = 2) or in self-medication (n = 27). The most frequent molecules were associated metronidazole-spiramycin, metronidazole, amoxicillin-clavulanic acid, ciprofloxacin, and ofloxacin.

3.8. Treatments in hospital

All purulent gatherings were evacuated by puncture if small and by drainage if larger.

In 3 cases, a Sebilleau incision was made, with careful necrosectomy and lavage with oxygenated water and povidone-iodine. Extensive drainage on a mediastinal approach via thoracotomy was performed in 2 cases.

Parenteral antibiotherapy was administered until clinical improvement in symptoms was achieved and oral antibiotics could be substituted. Antibiotherapy associated:

- amoxicillin + clavulanic acid 100 mg/kg/day in 3 fractions, IM gentamicin 3 mg/kg/day: n = 37 patients;
- amoxicillin + clavulanic acid and gentamicin at the above doses, associated to metronidazole 1 g/day: n = 12 patients;
- ceftriaxone 8 mg/kg/day: n = 13 patients;
- moxifloxacin 400 mg/day: n = 8 patients

Mean hospital stay was 5 days (range, 3–12 days, except for 2 patients requiring ICU admission for mediastinal extension of CFC; both died despite intensive care and surgical debridement extending to the mediastinum).
4. Discussion

Although NSAIDs cannot be incriminated in CFC with absolute certainty, several series, including the present, tend to implicate them, if not as a direct causal factor then at least as promoting or aggravating CFC. Mathieu et al. [2], in a series of 45 patients admitted with CFC, found NSAID use in 44% of cases. Merle et al. [3] highlighted NSAIDs as promoting CFC, reporting a 76.46% NSAID rate, similar to the present findings but in a smaller series of only 17 patients presenting with odontogenic CFC; 8 presented mediastinitis, 4 of whom had taken NSAIDs, and 7 of whom died.

In a larger series of 94 CFC patients admitted to intensive care between 1995 and 2005, Shaikh et al. reported NSAID use in 80% of patients [4]. An association between cellulitis complicated by odontogenic mediastinitis and NSAID use was reported in several other studies [3–9].

Cellulitis other than cervicofacial has also been reported, with NSAIDs implicated in evolution toward fatal necrotizing fasciitis [10].

This correlation may be explained by the action mechanism of NSAIDs against inflammation, which is after all basically a nonspecific defense mechanism against microbial invasion.

NSAIDs inhibit the degradation of cellular arachidonic acid by the cyclooxygenase pathway, preventing production of thromboxane A2 and prostaglandin, which play an important role in cellular chemotaxis. NSAIDs thus oppose polynucleate cell and macrophage migration and phagocytosis.

They also reduce the early signs of inflammation, thus delaying consultation [11,12].

The harmful impact of NSAIDs in infection was borne out by experimental studies, including that by Solberg et al. on phenylbutazone, demonstrating impaired granulocyte activation, phagocytosis and intracellular destruction of streptococci and staphylococci in vitro [13].

However, while the clinical and in vitro role of NSAIDs in aggravating infection has been often reported [11], some animal studies found no significant difference between experimental groups with CFC taking diclofenac versus placebo [11,12].

However, these studies had very small samples (some 20 individuals per arm), and the origin of infection was subcutaneous injection, as opposed to odontogenic or oropharyngeal in the great majority of human series. The animal models fail to fully reproduce the anatomic and bacteriological conditions found as CFC risk factors in humans.

Even so, other animal studies confirmed the role of NSAIDs in aggravating cellular tissue infection [14].

In the USA, the Center for Disease Control and Prevention (CDC) advised against prescribing NSAIDs in non-controlled infection or at least performing systematic assessment within 48–72 hours to track evolution [1].

CFC affects all age groups, with a mean age at onset of about 40 years [15,16]. In the present series, mean age was 33 years – probably due to the younger age pyramid found in Morocco. Pediatric forms are much less common, as in the present series with only seven 8–15-year-old. This may be due to the absence of certain CFC risk factors such as smoking and alcohol consumption. There have, however, been several reports of extensive CFC in children, including mediastinal extension [17]. Mediastinal extension may be primary in certain particularly aggressive forms (with weakened diathesis or use of NSAIDs) or following late or deficient management. It is facilitated by conjunction of cervical apeneu- roses into routes of infection. Infection from the last mandibular molars may directly contaminate the cervical and para-tonsillar regions (also known as anterior subparotid or pterygopharyngeal), which represent a strategic crossroads for extension to other cervical spaces and the mediastinum via the vascular route and detachable Reinke’s space.

CFC affects males more than females. Umeda et al. [18], in a review of 125 cases, reported a sex ratio of 3:1; in the present series there was likewise male predominance.

In the present series, the main CFC risk factor, other than NSAIDs, was diabetes (27.41%). Most of these patients had poor glycemic control. Diabetes is a known factor of immune
dysfunction [18–21], with elevated risk of non-specific infection [19]. Apart from infection of the extremities, cellulitis is one of the most common infections in diabetes [21], especially with infection sites such as tooth decay and dental apical granuloma.

Other immune system risk factors include HIV infection, liver cirrhosis, kidney failure and heart failure [18], although these were not found in the present series.

CFC propagates by contiguity from a dental (70%) or pharyngeal (20%) entry point [2,22–24]. Other possible etiologies are cutaneous inoculation or periadinitis.

In the present series, origin was principally dental (87.14%), a slightly higher rate than in the literature. This may be due to deficient oral and dental hygiene or to low socioeconomic status.

Extensive CFC is, as stressed above, an infection by contiguity, traveling along the fascias and communications of the face and neck [1]. Necrosis first involves less well-vascularized and oxygenated tissue such as fascia, extending to better vascularized tissue such as subcutaneous fat and muscle [1].

Infection is usually multisomatic, usually both aerobic and anaerobic [1,24,25], with synergic action: aerobic bacteria exhaust the oxidative defenses of immune cells (macrophages, granulocytes and monocytes), favoring the development of anaerobic bacteria [1].

The most frequent pathogen is Streptococcus pyogenes, although other strains have also been isolated: Enterobacter, Fusobacterium, Bacteroides, and Staphylococci [24]. One study found as many as 11 different strains in a single patient [25].

In the present series, 10 samples indicated multibacterial coccus and Gram-negative flora. The other, negative, findings may have been due to antibiotics taken before admission.

The multimicrobial nature of CFC highlights the interest of early broad-spectrum probabilistic antibiotherapy awaiting bacteriology and the antibiogram [24,26]. However, medical treatment alone cannot be curative as the purulent gatherings contained within necrotic tissue are disconnected from the vascular system, preventing diffusion of antibiotics, even if parenteral. In the present series, primary broad-spectrum probabilistic antibiotherapy was implemented and followed, whenever necessary, by drainage and more or less complete surgical debridement.

Mortality in the literature ranges between 19 and 40% [24], illustrating the extreme seriousness of this infection; in the present series, the rate of cure was 98.59%. Two deaths followed extensive mediastinal involvement.

5. Conclusion

Cervicofacial cellulitis is a serious infectious emergency requiring rapid adapted treatment.

Non-steroidal anti-inflammatory drugs impair immune system functioning and mask clinical presentation, delaying diagnosis and thus constituting a real risk factor for aggravation.

We would like to stress the fact that, although the present series showed a strong correlation between NSAIDs and CFC, this does not prove causality (because of possible recruitment bias and the routine prescription of NSAIDs), but at least it should be seen as an aggravating factor, invoking the precautionary principle.

Thus many health authorities, including the American CDC, recommend selective replacement of NSAIDs by the usual analgesics and antipyretics.

The present study is a call for all those involved in the ENT sphere (ENT specialists, maxillofacial surgeons and dentists) and community physicians to rationalize their NSAID prescriptions, and for strict respect of the indications for this class of drug.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References